# EXHIBIT E

# SUPPLEMENTAL REPORT OF JANET ARROWSMITH-LOWE, M.D.

I am a physician licensed to practice in the state of New Mexico. I am board certified in Internal Medicine, an elected Fellow of the American College of Epidemiology, and an elected Fellow of the American College of Physicians. I received my undergraduate degree at Duke University in 1972 and obtained my medical degree from Tulane University School of Medicine in 1979.

I have 11 years of experience with the United States Food and Drug Administration (FDA). I was a Medical Review Officer in the Division of Blood and Blood Products in the FDA Center for Biologics Evaluation and Research at FDA and in the Division of Antiviral Drug Products in the Center for Drug Evaluation. In both of these positions, I was responsible for reviewing premarket NDAs. I served as a Staff Epidemiologist in the Office of Epidemiology and Biostatistics at the FDA. In this position, I monitored the postmarket safety and effectiveness of marketed drugs, and I served as Consultant to the Centers for Drug and Biologics Evaluation and Research on epidemiologic issues and problems. Further, I was Acting Director of the Office of Surveillance and Biometrics in the Center for Devices and Radiological Health at the FDA. I was also an Epidemic Intelligence Service Officer at the National Centers for Disease Control (CDC) and Prevention in Atlanta, Georgia. In this position, I participated in CDC and FDA epidemiologic investigations of problems of national and regional interest.

I charge $500 per hour for regulatory consultative services as well as deposition and trial testimony.

I incorporate, in its entirety, here by reference my first expert report in this matter.

A list of materials considered for this Supplemental Report is attached as Exhibit 1. My current CV, including an updated list of cases in which I have testified as an expert over the past four years is attached as Exhibit 2.

I reserve the right to review and rely upon subsequent literature and reports filed by other experts. I have read and reviewed an excerpt of Supplemental Report of Dr. Sheila Weiss Smith and the Supplemental Report of Dr. Robert Gibbons, and I adopt and incorporate by reference the contents of those reports.

In this Supplemental Report, I am responding to new opinions and testimony of plaintiffs' experts and FDA's statistical review and evaluation of suicidality with antiepileptic drugs that were expressed subsequent to my first report. Specifically, I respond to new opinions and analyses set forth by Dr. Cheryl Blume and Mr. Keith Altman. I also offer opinions regarding Pfizer's conduct in the development, testing and labeling of Neurontin, which were not part of my general causation opinions in my first report. I hold the opinions expressed in this Supplemental Report to a reasonable degree of medical and scientific certainty, and these opinions are based on my education, training, experience, and my review of the relevant scientific and medical literature.

FDA ANALYSIS OF ANTIEPILEPTIC DRUGS

In early 2005, FDA began to investigate the question of suicidality for antiepileptic drugs ("AEDs") when a manufacturer, other than Pfizer, of a particular AED presented analyses of its placebo-controlled clinical trials that it believed suggested an increased incidence of suicidality in patients taking the drug. At that time, FDA decided to examine the controlled clinical trial data for 11 AEDs (carbamazapine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide). The results of this analysis were published on May 23, 2008 in a Statistical Review and Evaluation, and discussed in detail at an Advisory Committee meeting held on July 10, 2008.

I agree with FDA's decision to analyze only randomized placebo-controlled clinical trial ("RCT") data in this analysis. I also agree with FDA that post-marketing spontaneous adverse event data are inappropriate for a study of suicidality in the population of patients taking AEDs, as such patients have a high background rate of suicide. As Dr. Russell Katz of FDA pointed out at the July 10, 2008 Advisory Committee meeting,

> "...we had long ago decided that postmarketing data are not the right data to look at, or we don't believe that these sorts of things where there is a high background rate of suicidality so defined in these populations, I think that we have concluded that postmarketing data is uninterpretable, and that is why we went to placebo-controlled trials." (FDA Advisory Committee Transcript, July 10, 2008 at p. 103) .

Thus, contrary to the assertions made by plaintiffs' expert, Dr. Cheryl Blume (See Blume Declaration at ¶ 23), FDA concluded that post-market adverse event reports would not be appropriate data to use to study any potential link between suicidality and AEDs. The assertions contained in the declarations filed on behalf of Dr. Blume and Mr. Altman that analyses of disparate adverse event reports would have alerted Pfizer to a signal for suicidality resulting in a labeling change, including new warnings, are not supported by the evidence or sound post-marketing surveillance practices.

FDA identified 199 studies that met the trial inclusion criteria for this analysis. These studies included a total of 43,892 patients (27,863 on active treatment and 16,029 on placebo). FDA found that, overall, suicidality events occurred in 0.37% of patients on treatment and 0.22% of patients on placebo. This translated into a statistically significant odds ratio ("OR") for suicidality events of 1.80 (95% CI, 1.24 – 2.66).

FDA concluded that "there is a signal for increased suicidality for the class of AEDs" and that the "results for individual drugs were generally consistent with the overall result." It is unclear, however, what basis FDA has for concluding that the results were "generally consistent" among the 11 AEDs. Examination of the graph of individual odds ratios, presented on page 24 of the Statistical Review and Evaluation, shows that only 2 AEDs, lamotrigine and topiramate, had statistically significantly increased odds ratios. The remaining 8 AEDs (felbamate could not be analyzed because it had no events in either treatment arm) all had odds ratios that were not

statistically different from 1.0. Specifically, gabapentin (Neurontin) had an odds ratio of 1.57 with a 95% confidence interval of 0.12 – 47.66. Because the 95% confidence interval encompassed 1.0, the odds ratio for Neurontin was not statistically different from 1.0, and, as such, provides no evidence of an increased risk for suicidality. Thus, this analysis of the RCT data shows that there is no increased risk for suicidality for Neurontin. Topiramate and lamotrigine have, by far, more suicidality events than the other AEDSs (40 events and 27 events, respectively); the events from these two AEDs comprise 64% of the total number of events in this analysis (67 out of 104 events). The magnitude of the effect of these two AEDs on the overall analysis likely accounts for the overall odds ratio being statistically significantly greater than 1.0. FDA's use of the term "generally consistent" ignores the fact that 9 of 11 AEDs showed no increased risk for suicidality.

Similarly, FDA's overall risk difference analysis (which includes zero event studies) showed a statistically significant risk difference of 1.79 (95% confidence interval, 0.70 – 2.87). However, as with the odds ratio analysis, only lamotrigine and topiramate had risk differences that were statistically significantly increased from 0. Neurontin RCT data revealed a risk difference of 0.28 with a 95% confidence interval of -1.37 – 1.92. Because the 95% confidence interval encompassed 0, the risk difference for Neurontin was not statistically different from 0. Thus, this separate analysis of the RCT data again shows that there was no increased risk for suicidality for Neurontin.

There are a number of methodological flaws in FDA's analysis. When performing a meta-analysis, such as the one performed by FDA, assessing heterogeneity of trial results is a critical step to achieving accurate results. FDA stated that it used "Zelen's test" to examine between-trial heterogeneity, but it also stated, "because of the small number of events, it was expected that there would be little power to detect heterogeneity of the odds ratio across trials." Statistical Review and Evaluation at p. 15. Thus, the lack of any adequate assessment of heterogeneity leads me to question the validity of the overall results of this meta-analysis.

Another flaw in this analysis is the use of statistical methods that required FDA to eliminate any study with zero events in both the treatment arms of the trials. Such a method will bias the results in favor of increased risk for patients treated with the drug, as it will exclude those trials where there may be no difference in risk between drug-treated and placebo-treated patients. FDA proposed to account for the effect of excluding zero-event trials by performing a risk difference analysis. However, through an oversight in preparing the Statistical Review and Evaluation, it is impossible to tell the difference in events included in these two analyses. Specifically, comparing the sample sizes for the odds ratio analysis on page 24 (which would exclude zero-event trials) to the risk difference analysis on page 26 (which would not exclude zero-event trials), one can see that the sample sizes are identical. Thus, it is impossible to assess the magnitude of the effect of excluding zero-event trials.

Yet another flaw in FDA's analysis is the stratification of the data by "drug groups." Here, FDA chose 3 groups of drugs, based on a purported mechanism of action of the drug: sodium channel blocking drugs, GABAergic drugs and GABAmimetic drugs, and carbonic anhydrase inhibitors. The problem with this sub-group analysis is that 1 AED, topiramate, appears in all 3 groups. This is particularly troublesome because topiramate had far more events than any other AED (40 events in drug-treated patients). Similar to its influence on the overall

odds ratio and risk difference analyses, topiramate, being in all 3 sub-groups, is likely solely responsible for the statistically significant odds ratios presented on page 32 of the Statistical Review and Evaluation.

Another important consideration was raised by a committee member during the July 10, 2008 Advisory Committee that to conduct an accurate assessment of the risks and benefits of AEDs, all sources of morbidity and mortality associated with these drugs should be considered along with suicide or suicidality:

> Dr. Hennessy: To me it would help to put it in perspective to know whether other categories of death differed. In other words was there an attempt to look at all-cause death between the two groups of the meta-analysis? In some senses we would – if the only difference was suicide that would probably be washed out by other causes of death. On the other hand if the drugs cause beneficial affects that reduce the risk of death through other mechanisms, that would be important to know. And I'd like to hear data on that if we have it.
>
> Dr. Levenson: We did not collect any data on all causes of death. We do not have that data. July 10, 2008 Advisory Committee meeting transcript at p. 102.

For instance, carbamazapine is associated with several serious and life threatening adverse events including hepatotoxicity and aplastic anemia. To consider one risk in the absence of consideration of all risks and benefits hampers the utility of the FDA analysis and fails to fully account for the public health risks and benefits of these drugs.

The absence of the context of risk and benefit and the methodologic flaws in FDA's meta-analysis profoundly influence the inferences that may be drawn from the results. This is especially true for any attempts to draw inferences from these data that Neurontin, itself, causes or contributes to suicidality. Plaintiffs' experts have used FDA's AED analysis to support their opinions that Neurontin has the capacity to cause suicidal behavior. However, it is scientifically unsound to draw such an inference. The FDA meta-analysis was not designed to test either the hypothesis that AEDs cause suicide, or the hypothesis that Neurontin causes suicide. This issue was addressed at the Advisory Committee meeting and Dr. Levenson confirmed that the analysis applied to the entire data set of 11 AEDs:

> Dr. Twyman: Let's assume that the effect is generalizable to the class of AEDs. But if you look at the compounds individually, could one draw the conclusion individually that compounds have a risk, or do you need to the entire data set of all the AEDs put together in order to draw the conclusion that AEDs have a signal?
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> Dr. Levenson: I would say we need the entire data set in this case. July 10, 2008 Advisory Committee meeting transcript at p. 183 – 184.

Thus, the most that may be said about this meta-analysis is that it suggests an association between AEDs, as a class, and suicidality relative to placebo. Plaintiffs'

experts have improperly extrapolated the FDA's findings by saying that these data suggest that Neurontin causes or is capable of causing suicidality.

It is important to understand that FDA's meta-analysis was not based on a prospectively designed randomized clinical trial with suicidality as an outcome. This meta-analysis was based on a heterogeneous group of trials which were never intended to be combined for analytic purposes. Rather, FDA requested that certain sponsors submit data from previously conducted randomized clinical trials regarding events of suicide or suicidal behaviors. The events sought by FDA for the meta-analysis were not collected prospectively according to a predetermined protocol. Thus, FDA's meta-analysis was not designed to replace a prospective, randomized controlled clinical trial. Because the events to be analyzed by FDA were retrospectively captured and because different patient populations and drugs were included in the analysis, suicidality events could not be verified or validated. This could introduce an ascertainment bias into FDA's meta-analysis. Randomized placebo-controlled clinical trials are designed to minimize and monitor for potential biases in assessing the study outcome. However, because suicidality was not a study outcome in any of the clinical trials analyzed by FDA, the studies would not have had a protocol to prospectively monitor, identify, and validate suicidality events.

Perhaps more importantly, the results of the FDA meta-analysis do not support plaintiffs' assertions that Pfizer missed a signal for suicidality. Also, FDA's meta-analysis does not support plaintiffs' experts' opinions that Pfizer should have implemented, on its own, a warning regarding suicidality. Such assertions ignore the fact that FDA used 199 RCTs, with 43,892 patients, from 11 different AEDs to show an association between AEDs and suicidality. The fact that FDA concluded that there was a signal for increased risk of suicidality with the entire class of AEDs does not suggest that Pfizer should have found a similar signal for Neurontin alone. In fact, FDA's own data show that there was not a statistically significantly increased risk for suicidality with Neurontin. Plaintiffs' experts also ignore the fact that the July 10, 2008 Advisory Committee concluded that the FDA's conclusions from its meta-analysis should apply to all currently approved chronically administered AEDs, including those not part of this analysis. Thus, any potential warnings that may be required by FDA regarding suicidality will apply to the entire class of AEDs, not just Neurontin. Pfizer, based on its own RCT and postmarket adverse event data and later confirmed in the FDA's meta-analysis, did not have a reasonable basis to add a similar warning to the Neurontin label.

Plaintiffs' experts have opined that Pfizer should have warned of the risks for suicidality in patients receiving Neurontin for off-label indications. As I explained in greater detail in my first report, FDA does not regulate the practice of medicine. This means that once a product is approved for marketing in the U.S., prescribers are permitted to prescribe or use the product as they feel is in their patients' best interests. Furthermore, had FDA believed that Neurontin posed an increased risk of injury only in certain patient populations using the medication off-label, it had the full authority to require Pfizer to include in the Neurontin labeling a specific warning regarding efficacy or safety concerns associated with off-label uses. 21 C.F.R. § 201.57(e) (April 2002). To date, FDA has not requested that this type of a warning be added to the Neurontin labeling and it is my opinion that such a warning would have been inappropriate and unsupported by the available clinical and postmarket adverse event data. In fact, in its meta-analysis of AEDs, FDA performed a sub-group analysis by trial indication and it found that although there was, for the overall group of AEDs, an increased risk for suicidality for the

labeled epilepsy indication (OR = 3.53, 95% CI = 1.28 – 12.10), but not for the off-label "psychiatric" indication (OR = 1.51, 95% CI = 0.95 – 2.45) or the "Other" category (which would include pain indications) (OR = 1.87, 95% CI = 0.81 – 4.76). Statistical Review and Evaluation at p. 33.

Both Dr. Blume and Mr. Altman assert in their declarations that by the fourth quarter of 2002, increases in serious adverse events were due to increases in off-label use. However, Dr. Blume and Mr. Altman only provide counts of adverse events. They fail to put the number of adverse events in the context of the number of prescriptions (which also increase significantly during this time period) or the background of suicide in the populations taking Neurontin (which are significantly elevated compared to the general population). In addition, Dr. Blume acknowledged in her first deposition that notoriety bias during this time period would affect reporting rates. Dr. Blume and Mr. Altman also failed to recognize the general increase in reporting of suicides during this time period (as described in detail by Dr. Sheila Weiss Smith in her Supplemental Report), including reporting in the literature of suicides by Poison Control Centers. Failure to account for these variables significantly limits the inferences that Dr. Blume and Mr. Altman may make based on simple counts of adverse events.

Plaintiffs assert that Pfizer should have added warnings of an increased risk of suicide to the Neurontin labeling. FDA had not required such warnings on the Neurontin label, which is consistent with the clinical trial and postmarket adverse event data for Neurontin. It was not until FDA decided to combine the randomized clinical trial data for 11 different AEDs that a signal for suicidality for the class of AEDs was proposed. Even then, the Advisory Committee voted to not include a Black Box warning in the labeling of AEDs; in fact, the Advisory Committee made no decisions regarding any specific warnings for suicidality for the group of AEDs considered, much less for Neurontin alone. If the Advisory Committee was not convinced of the needed clinical trial data from 199 studies from 11 different AEDs, there is absolutely no evidence to suggest that Pfizer, on its own, should have made changes suggested by plaintiffs' experts to the Neurontin labeling.

I have read the deposition transcript of Dr. Stephan Kruszewski (Oct. 16, 2008) and his suggested labeling for Neurontin. His suggestions specifically regarding Neurontin are without any basis or justification. For example, he suggests labeling that states, "[T]here are precursors to the enhanced risk of suicide, which may include irritability, restlessness, akathisia, sudden mood and behavioral changes when the drug is taken, and that those changes may occur acutely or chronically." Kruszewski deposition at 404:9 – 16. However, there are no data showing a statistically significant increased risk for these events with Neurontin, nor is there reliable evidence that these events are even precursors to suicidality. Dr. Kruszewski also suggests the following:

> "…the increased risk of suicidal ideation, suicidal thoughts, and completed suicides may increase with the ingestion of Neurontin by virtue of certain drug interactions. The drugs that change the maximum concentration of Neurontin have already been listed in the label, so I would not -- I would just reemphasize that certain drugs can increase excretion, increase metabolism, decrease excretion, decrease metabolism, and, therefore, give rise to an

enhanced Neurontin effect, which may or may not increase the risk of suicidal thoughts and suicidal acts." Kruszewski deposition at 405:1 – 15.

Again, Dr. Kruszewski does not base this labeling suggestion on any reliable scientific or medical evidence available today. There are no data to support Dr. Kruszewski's labeling recommendations.

The recommendations and voting by the Advisory Committee reflect regulatory and/or policy decisions based on the committee's concern of a signal suicidality of antiepileptics as a group of drugs. Nothing in the discussions or recommendations by the Advisory Committee are consistent with a position that FDA's meta-analysis provided reliable scientific evidence that the group of the 11 AEDs studies or any individual AED within that group were causality associated with suicidality.

PLAINTIFFS' EXPERTS CANNOT MAKE A VALID COMPARISON BETWEEN THEIR CRUDE COUNTS OF SPONTANEOUS ADVERSE EVENTS TO FDA'S META-ANALYSIS OF AED RANDOMIZED, CONTROLLED CLINICAL TRIAL DATA

Plaintiffs' experts, particularly Dr. Cheryl Blume, assert that the FDA AED meta-analysis supports their conclusions that Pfizer missed a signal for suicidality for Neurontin and that the meta-analysis is evidence that Neurontin causes or substantially contributes to suicidality. In both her original report and in her subsequent declaration, Dr. Blume presents simple tabulations of certain "negative mood and behavioral disturbance" and "psychobiologic" adverse events that she claims provide a signal for suicidality. This approach, however, differs from the approach taken by FDA in analyzing suicidality. Importantly, FDA concluded that post-market adverse event data were inappropriate for an analysis of suicidality. Additionally, FDA considered only completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation. See Statistical Review and Evaluation at p. 8. FDA never considered the various adverse events that Dr. Blume analyzed. There is no scientific basis to group adverse events such as hostility, aggressiveness, or depression in an attempt to assess a signal for suicidality. Pfizer should not be faulted for not performing the unscientific and unsubstantiated analyses such as those performed by Dr. Blume in her reports or her Declaration.

Moreover, FDA did not perform a causal assessment for suicidality in its analysis of the 11 AEDs. In its March of 2005 Guidance Document on Pharmacovigilance Practices, FDA sets forth factors that it will take into account when assessing whether a causal association exists between drug ingestion and an event. These factors include, strength of the association, temporal relationship, consistency of the findings across available data sources, evidence of a dose-response, biologic plausibility, seriousness of the event, potential to mitigate the risk, feasibility of further study, and degree of benefit provided by the product. March of 2005 Guidance Document on Pharmacovigilance practices at p. 18. In its analysis of the prospective randomized clinical trial data for 11 AEDs, FDA did not undertake such a causal assessment. Dr. Blume or Mr. Altman have not performed any such analysis of the randomized clinical trial data for Neurontin or the 11 AEDs. At most, FDA's meta-analysis merely sets forth the hypothesis of a potential signal or association between 11 AEDs and suicidality. Importantly, the FDA analysis does not set forth the hypothesis of a potential signal or association between

Neurontin and suicidality; in fact, FDA found no statistically significant association between Neurontin and suicidality (based on odds ratio and risk difference calculations). Because the randomized clinical trial data for Neurontin did not show any association with suicidality, there is no sound scientific basis to even undertake a causal assessment, as set forth in FDA's Guidance Document on Good Pharmacovigilance Practices. Thus, it is inaccurate and incorrect for Dr. Blume and Mr. Altman to suggest that FDA's meta-analysis supports a causal role of Neurontin for suicidality.

PLAINTIFFS' EXPERTS' ASSERTIONS THAT PFIZER MISSED A SIGNAL FOR SUICIDALITY WITH NEURONTIN ARE BASED ON UNRELIABLE AND UNSCIENTIFIC METHODS

Interestingly, Dr. Blume ignores the peer-reviewed medical literature showing that, in placebo-controlled studies, Neurontin actually has beneficial effects on the "psychobiologic" events that she highlights as being predictive of suicidality. Rowbotham, et al., (JAMA, 1998), a paper cited in Dr. Blume's report, presents a placebo-controlled trial that examined the effect of Neurontin on psychobiologic conditions. These investigators found that treatment with Neurontin resulted in significant reductions in total mood disturbance, depression-dejection, anger-hostility, and confusion-bewilderment. Thus, this placebo-controlled trial clearly shows a beneficial effect on the same psychobiologic events that Dr. Blume contends are worsened with Neurontin. The key difference between the two types of analysis is that the placebo-controlled study used comparison between Neurontin and a control group, as well as statistical analysis to show differences between the two groups. Dr. Blume's analysis involves nothing more than eye-balling counts of various adverse events, without any comparison group or statistical analysis. As I stated in my first report in this matter, "...true signals should emerge from clinical judgment and that statistical algorithms, such as PRRs, should be used as supplements to clinical and epidemiological judgment, not replacements." Brian L. Strom, "Evaluation of Suspected Adverse Drug Reactions – Reply," JAMA 293:1324 – 1325 (2005).

Additionally, Dr. Blume makes no attempt to analyze the adverse event reports beyond the simple tabulations that she made, which means that Dr, Blume has not followed generally accepted methodology in interpreting the information. Dr. Blume asserts in her declaration that the protocol developed to gather information regarding suicidality, the "Gabapentin Capture Aid," could have been used by Pfizer to "capture information regarding suicidality as early as 1994." Blume Declaration at ¶ 38. Dr. Blume mischaracterizes and misuses this document. The purpose of the Gabapentin Capture Aid was to "systematically collect and assemble all available information...involving adverse events of special interest" and to provide "additional lines of inquiry designed to gather supplementary data." NREXE2091004141 at p. 1. The Gabapentin Capture Aid was to "help to ensure accurate and timely characterization of the reported adverse events including the relative contributions of potential etiological factors to the occurrence of the selected events." NREXE2091004141 at p. 1. Nowhere in this document is there any statement that the data collected through use of the Gabapentin Capture Aid should replace clinical and medical judgment in interpreting the data collected. The Gabapentin Capture Aid served as an additional tool to help gather data on suicidality, but Pfizer performed diligent pharmacovigilance well before the implementation of the Gabapentin Capture Aid.

Dr. Blume further claims that Pfizer failed to analyze adverse events by grouping terms as suggested by the Gabapentin Capture Aid and rather analyzed those events occurring at less than 1% of the total number of events. The Gabapentin Capture Aid does not suggest grouping of adverse event terms or of analyzing adverse event terms, but rather it lists terms that trigger the use of the Aid when collecting the data. Also, Dr. Blume fails to acknowledge the clinical and medical judgment that Pfizer used in assessing all adverse events, not merely those that reach the 1% level. See Pacella deposition at 178:19 – 22. Per the deposition testimony of Pfizer Core Labeling employee, Christopher Pacella, the reason why preferred terms for suicide or suicide attempt were not included in the labeling is that "based on the post-marketing data that [Pfizer] reviewed, it did not meet the threshold that was set forth to evaluate that particular event based on medical judgment and clinical judgment by the medical experts." Pacella deposition at 208:25 – 209:11. Dr. Blume performed no analysis beyond mere counts of adverse events to analyze her results. The lack of any clinical or medical review of Dr. Blume's counts of adverse events invalidates opinions based on those counts; the process of grouping adverse event terms is meaningless without clinical and medical review of the events. Pfizer properly conducted clinical and medical review of the adverse event data regarding suicidality. Pfizer's use of the Gabapentin Capture Aid was responsible and diligent, as this tool was used to gather the most possible information to better assess whether Neurontin could have played a role in suicidality. Pfizer's judgment that the adverse event data did not present a signal for suicidality was consistent with FDA's subsequent review of the Neurontin and other AED clinical trial data.

In paragraph 29 – 30 of her declaration, Dr. Blume asserts that adverse events from uncontrolled studies are "considered by the FDA to be important in assessing the overall safety of a drug." Dr. Blume claims to rely upon the deposition testimony of Pfizer regulatory affairs employee Janeth Turner for the proposition that FDA considers both controlled and uncontrolled studies to evaluate safety of the drug. However, Dr. Blume misconstrues this general comment about studies that FDA may consider for safety as applying specifically to Neurontin and suicidality. This assertion has no basis. FDA considers only prospective randomized placebo-controlled data to be appropriate for such an analysis.

Dr. Blume states that Mr. Altman's methods have been vetted and approved by FDA following approval of two NDA's and review of a third NDA in which Mr. Altman had performed analyses. Dr. Blume states that FDA has never rejected Mr. Altman's submissions. Blume Declaration at ¶10. This misstates FDA process of reviewing NDA's. FDA takes data from the NDA and performs its own independent evaluation and analysis of the safety data and it does not grade or review of a particular section of an NDA. The purpose of an NDA is to present FDA with evidence that a drug's benefits outweigh its risks, and the use of summary tables in an NDA are to facilitate FDA's review of the relevant data. These tabular presentations do not, in and of themselves, permit a reliable analysis of causation, as suggested by Dr. Blume and Mr. Altman. While such descriptive statistics are often provided as context or background within NDA's and other regulatory submissions, they do not provide any proof of an association. To argue that the mere inclusion of similar data tables within NDA's or Integrated Safety Summary reports as evidence that they are a valid method to evaluate risk, much less the cause, of a particular adverse event is without any scientific merit. Absent the ability to review the MORs for the data presentations made by Mr. Altman, there is no way to determine whether FDA agreed or disagreed with the tables he produced.

In paragraph 21 of her declaration, Dr. Blume makes the statement, "There is no epidemiologic evidence that a causal relationship does not exist between Neurontin and suicidality." This statement is inaccurate on a number of grounds. It is not surprising that such evidence does not exist, because scientific evidence is not developed in that manner. No scientific study would ever be designed to test the hypothesis that a relationship between Neurontin and suicidality does not exist. Rather, all scientific studies begin with the null-hypothesis: the hypothesis that there is no difference between treatment groups (e.g., no difference in suicidality between Neurontin and a control treatment) and are powered such that it would be likely that the null hypothesis could be rejected, if the data support that conclusion. Then, experiments and statistical analysis are performed to determine whether the null-hypothesis can be rejected (i.e., there is a difference in suicidality between Neurontin and a control treatment). More importantly, the epidemiologic data presented by FDA in its AED meta-analysis does indeed show evidence that a causal relationship does not exist between Neurontin and suicidality. Examination of the Neurontin-specific data shows that there is no statistically significant increase in odds ratio or risk difference. Dr. Blume argues that the Neurontin clinical trial data are too small to detect a risk for suicidality. However, the data for lamotrigine, which did show a statistically significant increased risk for suicidality, had similar number of patients as Neurontin in both the treatment group (2865 for lamotrigine versus 2903 for Neurontin) and placebo group (2070 for lamotrigine versus 2029 for Neurontin). If the risk for suicidality at the level seen for lamotrigine was present for Neurontin, the Neurontin clinical trials were sufficiently powered to detect that risk. Thus, the available data show that one cannot reject the null hypothesis that there is no difference in risk for suicidality between Neurontin and placebo treatment.

Plaintiffs' expert Cheryl Blume, PhD refers to "Regulatory documents from the FDA" (Blume report page 10) as reflecting Pfizer knowledge about safety issues related to Neurontin. As part of the initial NDA review and approval process, FDA medical officers reviewed safety information available in Integrated Summary of Safety ("ISS") and four safety updates. The document from which Dr. Blume quotes is the Medical and Statistical Review for the initial approval of Neurontin as adjunctive treatment in refractory partial seizures with and without secondary generalization in adults with epilepsy. This document is an archival document intended to record the medical and statistical reviewers' bases for their recommendation that a new drug product be approved, not approved or approvable and is also commonly referred to as a medical officer's review or MOR. The FDA's final decisions about the safety and effectiveness of an approved new drug are found in the approval letter and the approved labeling. Dr. Blume is mistaken if she believes that the MOR reflects FDA's final assessments of safety and effectiveness of a drug product. The MOR is not provided to a sponsor as a "regulatory document". In fact, that specific MOR is usually only available via a Freedom of Information request.

In the case of Neurontin, the FDA's assessments of safety and efficacy were vetted during presentations to and discussions by experts on the Peripheral and Central Nervous System Drugs Advisory Committee's held on December 14 and 15, 1993. Further information about FDA's assessments of a drug product's safety and effectiveness are evident during labeling discussions. The manufacturer was correct in not inferring from the statements in the MOR that the clinical trial data, at the time Neurontin was initially approved, raised a signal for suicidality or depression.

PLAINTIFFS' EXPERTS' INCORRECTLY STATE THAT THE NEURONTIN POSTMARKETING ADVERSE EVENT DATA SUPPORT A CAUSAL ASSOCIATION BETWEEN NEURONTIN AND SUICIDALITY

In paragraph 23 of her declaration, Dr. Blume states that adverse event reports "support the existence of a causal link between patients who take Neurontin and suicidality." Dr. Blume incorrectly points to her Exhibit C, slide 4 of a slide presentation by Rachel Sobel from Pfizer's Global Epidemiology, as support for this assertion. Dr. Blume completely misrepresents this slide. That slide includes clinical data, epidemiology and spontaneous reports as being "necessary to evaluate a drug's safety profile." Dr. Blume ignores Pfizer's important caveat, shown on the same slide, that spontaneous reports represents the least scientific rigorous data. This is especially true for spontaneous report data involving suicidality, as pointed out by Dr. Russell Katz at the July 10, 2008 Advisory Committee meeting on AEDs and suicidality, who said the postmarketing data were "uninterpretable" in the setting of suicidality. July 10, 2008 Advisory Committee meeting transcript at p. 103.

Dr. Blume further claims that "the collection of case report information is a recognized method to evaluate whether there is a reasonable inference that a drug can cause an adverse event in a particular individual." Blume Declaration at ¶ 23. Here, Dr. Blume confuses the practice of causality assessment of adverse events in individual patients with the scientifically rigorous procedure of determining whether an association between ingestion of a drug and the occurrence of an adverse event. For each clinical trial adverse event, investigators are required to provide their individual assessment as to whether the drug may have caused or contributed to the reported adverse event for that one patient. It is important to remember that these assessments reflect a single investigator's opinions and may be subject to a number of biases. In fact, when dealing with subjective events, such as depression, suicidal ideation or other psychiatric events whose presence is reported by the patient rather then being diagnosed through an objective test, it is difficult to assess whether a particular drug causes the event:

> "Non-specific subjective complaints, such as weakness, lethargy, altered consciousness or difficultly concentrating, are the most difficult symptoms to assess. When the same subjective effects are reported in response to several pharmacologically unrelated drugs, it is unlikely that a physiological mechanism is responsible." Knowles, et al., Can. J. Clin. Pharmacol. 9:149 – 153 (2002).

This precludes the use of clinical trial causality assessments, which are made with limited patient information, as being a scientifically rigorous assessment of causation. Rather, compilation of those data, with rigorous statistical comparisons, are necessary to assess whether an agent is a capable of causing an event. This type of scientifically rigorous analysis, which involves a determination on a population level, not an individual level, requires careful consideration of factors (temporal relationship, strength of the association, dose-response, replication of the findings, etc.) that epidemiologists use in making judgments about causation. Dr. Blume performs no such rigorous scientific analysis.

In support of their position, plaintiffs and Dr. Blume incorrectly point to FDA's March of 2005 "Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoedpimiologic Assessment" as support for the notion that causality assessments in individual patients supports a causal association between Neurontin and suicidality. There, FDA has stated,

> For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g., stroke, pulmonary hypertension). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event. "Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoedpimiologic Assessment" at 7.

Dr. Blume fails to consider this direction from FDA in her analysis of Neurontin postmarketing adverse events. She did not perform any "rigorous pharmacoepidemiologic studies" or any other type of "appropriate follow-up" of the Neurontin data. She does nothing more that merely present raw counts and simple percentages then she draws unsubstantiated conclusions regarding a link between Neurontin and suicidality based on those counts.

Despite the fact that plaintiffs and Dr. Blume assert that the 2005 FDA guidance document is the basis for their "causal" analysis of postmarketing data, they do not follow the procedures set forth for "interpreting safety signals." FDA recommends that "after identifying a safety signal" one should "conduct a careful case level review and summarize the resulting case series descriptively. "Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoedpimiologic Assessment" at 17. FDA also recommends that one either "employ data mining techniques" or "calculate reporting rates for comparison to background rates" to "further characterize a safety signal." Id. Dr. Blume does neither. In contrast, Pfizer did properly perform a substantial clinical review of the postmarketing data, taking into account the background rate of suicidality of the patient populations taking Neurontin, in assessing any possible link between Neurontin and suicidality. Parsons' Report, 2004, Pfizer_Regulatory_001621.

In addition, a number of spontaneous reports of suicidality were derived from literature reports from Poison Control Centers. A substantial number of these reports are incomplete and provide either no or inadequate medical information to make any meaningful judgment regarding causality for purposes of labeling. This is yet another reason why the spontaneous adverse event data do not provide a sufficient basis to institute a labeling change for suicidality.

PLAINTIFFS' SO-CALLED "RED FLAGS" DO NOT SUGGEST A SIGNAL FOR SUICIDALITY WITH NEURONTIN THAT WOULD HAVE WARRANTED A LABELING CHANGE

Plaintiffs suggest that a combination of information ("red flags"), when considered together, provides sufficient evidence that Neurontin has the biologic capacity to cause suicidality and that the Neurontin label should have been changed to include a warning pertaining to suicidality. Daubert hearing transcript, Day 2 at 197:7 – 200:20. First, much, if not all, of this information was submitted to and considered by FDA over the life of this product. Specifically, information pertaining to dechallenge/rechallenge events, spontaneous adverse event reports, FDA's clinical reviews of Neurontin between 1992 and 2003, including FDA's consideration of clinical trial adverse events and withdrawals, considered together or separately did not suggest that Neurontin was associated with suicidality and therefore there were no changes that should have been made to the warnings in the labeling. I have addressed many of the problems with this evidence in this report, as well as in my earlier report.

For example, the suggestion that clinical trial withdrawals that were submitted to FDA in various documents, including an ISS cited by Dr. Blume, would have triggered a signal of suicidality is without merit for a number of reasons. First, plaintiffs' experts' analysis of clinical trial withdrawals is post-hoc collection of numerous adverse event terms that is misleading and intentionally biased against Neurontin. Second, there is no scientifically accepted connection between the various adverse event terms cited by Dr. Blume and suicidality. Third, the various tables setting forth clinical trial withdrawals are incomplete and, when appropriately configured, do not demonstrate any consistent pattern that would raise issues for suicidality. Moreover, the use of the purported PRR analysis of adverse event terms from various adverse event databases is deficient in its methods and, in my opinion, do not demonstrate a signal for suicidality. Finally, the FDA alert and subsequent meta-analysis provide no basis to suggest that Pfizer's Neurontin label was inadequate in regard to suicidality and, in fact, confirms the various labeling decisions made by Pfizer and FDA.

## CONCLUSIONS

Although FDA has determined that the results of its analysis of suicidality and AEDs applies to all AEDs (including those not contributing data to the analysis), there are no independent analyses that confirm that Neurontin is associated with suicidality. The RCT data for Neurontin are not consistent with the FDA's overall risk estimates for suicidality. It remains my opinion that the Neurontin package insert appropriately summarized and disclosed safety and effectiveness information to the prescribing public. It is my opinion that physicians and other prescribers were provided with the essential information needed to safely and effectively prescribe Neurontin, including appropriate information concerning reports of suicide, suicidal behavior and depression arising from the clinical trials populations and from patients receiving Neurontin following market approval. None of plaintiffs' "red flags," taken together or individually, suggest a signal existed for suicidality. It is my opinion that the package insert fully complied with FDA regulations in terms of the information required and the information provided. FDA's meta-analysis of 11 AEDs does not alter my opinions regarding Neurontin labeling. It is my opinion that, all times, Pfizer acted reasonably and appropriately in collecting, analyzing and disseminating data regarding Neurontin and suicidality.

Dated: November 7, 2008

Janet Arrowsmith-Lowe, M.D.